ASPECTS OF OPIOID REGULATION AND EFFECTS ON OPIOID USERS

by

Daniel J. Bolton

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STATEMENT OF DISSERTATION APPROVAL

The dissertation of **Daniel J. Bolton**

has been approved by the following supervisory committee members:

Christina Porucznik	, Chair	**September 16, 2015** Date Approved
Joseph Stanford	, Member	**September 16, 2015** Date Approved
Lisa Gren	, Member	**September 16, 2015** Date Approved
Leslie Francis	, Member	**September 16, 2015** Date Approved
Barbara Insley Crouch	, Member	**September 16, 2015** Date Approved

and by **Stephen C. Alder** , Chair/Dean of

the Department of **Division of Public Health**

and by David B. Kieda, Dean of The Graduate School.

ABSTRACT

Opioid drugs prescribed legally have a great potential for both benefit and harm. The present study examines the potential impact of regulatory changes on opioid prescribing and use as well as differences in opioid use between men and women and among different age groups.

The Utah All Payer Claims Database (APCD) includes data that illuminate the effect of proposed changes to opioid prescribing guidelines. The data were analyzed in a cross-sectional study, with a study population of persons who were dispensed opioids in Utah between 2011 and 2013.

Between 21% and 44% of prescriptions would likely generate increased demands on provider time and other resources under new guidelines. Women and older Utahns are dispensed disproportionately large numbers of opioids. Men and women receive similar quantities of specific opioids, suggesting providers do not consider the impact of sex on opioid use. Review of the APCD data suggests possible improvements in data quality.

In a separate analysis, data from the Utah National Violent Death Reporting System (NVDRS) data were examined in a retrospective cohort study of decedents whose deaths involved prescription opioids. Deaths were analyzed by sex, by age group, and by number of causes of death recorded.

Women and men displayed different patterns of opioid use. Women were more likely to die after taking drugs that may be considered less potent. Men were more likely to die after taking opioids that were obtained for other persons.

Some opioid deaths among older Utahns are probably not recognized as such because death may be attributed to comorbidities. Older opioid decedents are more likely to have committed suicide than younger decedents. Children who die after taking opioids are likely to have taken drugs obtained for other persons, which highlights the importance of drug safety. Opioid patients should be seen within their family and social contexts to promote their health and that of those around them.

Sex and age influence opioid use. The data also suggest that promoting effective opioid treatment requires broad perspectives on providers, patients, and patient contexts. Improved health care data quality will strengthen the results of health care research.

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CHAPTER 1

INTRODUCTION

The last twenty years have seen a threefold increase in opioid prescriptions in the United States (US). With less than 5% of the world population, the US consumed 99% of the world hydrocodone supply in 2007.[1] US emergency department (ED) visits related to opioid usage doubled between 2004 and 2008.[2] Prescription drug overdoses (including opioids and other drugs) are the leading cause of injury death in Utah[3] and in the United States[4] generally. Attempts to address the problem have included changes in regulations, education for providers and the public, and new treatments for those dependent on opioids. Despite these efforts, the rise in opioid use—and abuse—continues, and the US incurs significant costs as a result. Although opioid use has drawn the attention of many researchers, much remains unknown about this topic. Open questions include how opioid use differs between men and women and among different age groups and the possible impact of proposed changes in opioid prescribing practices.

1.1 Opioid prescription drugs

Opioids may be natural products of the opium poppy, such as morphine, or fully or partially synthetic drugs that mimic the effects of opium products. This study focuses on these opioids that are used in outpatient settings:

1. Buprenorphine
2. Codeine
3. Fentanyl
4. Hydrocodone
5. Hydromorphone
6. Meperidine
7. Methadone
8. Morphine
9. Oxycodone
10. Oxymorphone
11. Tapentadol
12. Tramadol

Not all of the drugs have the same analgesic effect. Opioids are usually compared to morphine as a measure of their effect. Hydrocodone is equivalent to morphine. Codeine, Meperidine, tapentadol, and tramadol provide less analgesia than morphine. Buprenorphine, fentanyl, hydromorphone, methadone, oxycodone, and oxymorphone provide more analgesia than morphine. Exact analgesic relationships depend on drug formulation and dosage.

Opioids work by attaching to opioid receptors found in the nervous system,

gastrointestinal system, and other areas of the body.[5] In addition to pain relief, opioids can cause nausea, constipation, drowsiness, and sexual dysfunction; some opioid users experience hyperalgesia. Other negative effects of opioid use for long-term users include the possibility of dependence and the need to take escalating doses of opioids to achieve the same analgesic effect.

1.2 Opioids and treatment of pain since the 1990s

In the late 1990s state medical boards began easing restrictions on the prescription of opioids for chronic, noncancer pain.[6] At the same time, the Federation of State Medical Boards developed Model Guidelines for the Use of Controlled Substances for the Treatment of Pain,[7] which influenced policy on pain treatment nationwide. A national trend recognized that pain had often been undertreated and that patients suffered needlessly as a result of the undertreatment.[8] Analysis of data from the 2012 National Health Interview Survey (NHIS) revealed that 25.3 million American adults suffer from chronic pain and almost 40 million experience severe levels of pain, respectively 11% and 17% of the US adult population.[9] The proportion of patients with chronic pain who can be effectively treated with opioids remains controversial.[10]

1.3 Rise in opioid use and consequences

Sales of opioid analgesics in the US quadrupled between 1999 and 2010.[11] A 2014 study found that two-thirds of ED visits for opioid overdoses involved prescription opioids.[12] Globally, pharmaceutical companies are estimated to have

produced more than 75 tons of oxycodone in 2012, up from 11.5 tons in 1999. More than 80% of this drug is consumed in the US.[11]

A 2011 study estimated the total cost of nonmedical use of prescription opioids in 2006 at $53.4 billion.[13] This figure was broken down into $42 billion for lost productivity, $8.2 billion for the criminal justice system, $2.2 billion for treatment, and $944 million for other medical issues that arise from abuse. The phenomenon has also caused unquantifiable costs, such as stress on family relationships.

Research suggests that there are significant differences between men and women who abuse opioids.[14] However, there has been limited attention to treatment for women opioid users. A 2013 report from the Centers for Disease Control and Prevention (CDC) notes that deaths in women from overdoses of prescription pain medications climbed more than 400% between 1999 and 2013, compared to a 265% rise among men during the same period.[15]

Opioid use in older adults is further complicated by the common problem of polypharmacy. These Americans are prescribed many medications that may not be carefully monitored or which they may not take as recommended. Research also shows that opioids are often underprescribed to older adults.[16]

Opioids used by older adults may have detrimental physical effects and can produce cognitive difficulties that further degrade the patient's quality of life. Moreover, deaths by opioid overdose may be undetected if older adult patients have comorbidities that could shorten their lifespans but that do not cause death in an individual case. Evidence that some overdose deaths in older adults are not detected would suggest the need for closer attention to opioid use to improve the

health of this group.

The most severe consequence of opioid use is an overdose that leads to death. Prescription drug overdose is the leading cause of accidental death in the US[4] and in Utah.[3] Overdose deaths involving opioids more than tripled in the US between 1999 and 2008, and opioids were involved in more than 40% of drug deaths in 2008, compared to about 25% in 1999.[17]

1.4 Strategies to address opioid misuse

Federal, state, and local authorities have explored a variety of avenues to address the overuse of opioids. New York City adopted guidelines for prescription of opioids by EDs.[18] Most states have established prescription drug monitoring programs (PDMPs) to track the opioids patients have received and reduce physician shopping.[19] Federal and state authorities have explored regulatory changes to reduce overuse. Drug manufacturers have developed new formulations of medications and new packaging to discourage abuse. Opioid prescribing guidelines are standards that guide providers who treat patients with chronic pain.

Prescribing guidelines may recommend reevaluation of a treatment plan if the patient takes a dose of opioids above a certain threshold. The threshold is usually expressed in terms of a morphine equivalent dose (MED), a common unit to compare different opioids. MED values are typically calculated by finding a dose of the opioid that is equivalent to 10 mg of parenteral morphine. Prescribing guidelines often specify a threshold MED measured in milligrams per day (mg/d MED).

The States of Washington and Ohio have recently revised their prescribing guidelines. The Ohio guidelines establish a threshold of 80 mg per day morphine equivalent dose (mg/d MED) as a point at which providers should reassess the therapy.[20] State officials have suggested that the recommendations in the Ohio guidelines will be made mandatory if the guidelines do not bring a reduction in the number of opioid prescriptions being written. By contrast, the Washington guidelines establish a 120 mg/d MED dosing threshold.[21] In 2015, the Centers for Disease Control and Prevention (CDC) announced that it would issue suggested prescribing guidelines. Proposals for these guidelines included dosing thresholds of 50 and 90 mg/d MED values.

Utah's Clinical Guidelines on Prescribing Opioids for Treatment of Pain were adopted in 2009.[3] Utah is now considering revisions to its Guidelines.

Another source of information for possible opioid misuse is the National Violent Death Reporting System (NVDRS). Utah is a participant in this program, which is administered by the CDC and which seeks to reduce the number of violent deaths by providing data to inform prevention. Data collected in Utah include information on intentional and unintentional drug overdoses. Utah was the first NVDRS participant to record deaths from overdoses.

1.5 The present study

The study has three aims. The first considers the possible impact of proposed changes in opioid prescribing guidelines on prescribing practices in Utah, excluding opioids used for inpatient treatment, breakthrough cancer pain, and opioid-tolerant

patients. Records from the Utah All Payer Claims Database (APCD) of prescriptions dispensed in the years 2011–2013 were analyzed to determine how many prescriptions fall within dosing threshold categories, based on the strength of the prescriptions (50, 80, 90, and 120 mg/d MED). The second and third aims both examine data from deaths in Utah related to opioid overdoses. The second aim reviews overdose death data overall and by sex of decedents, and the third aim analyzes the data by the age of decedents.

This project provides essential knowledge in several areas of opioid research. Comparison of prescribing guidelines with dispensing records illuminates how changes in guidelines could affect prescribing practices.

The study represents a first use of APCD data to examine dispensed opioid prescriptions for information about aspects of opioid use. Similarly, NVDRS data for the years under study have not yet been reviewed for insights on overdose deaths among different age groups and by sex. The study results provide guidance for future research using the data and for potential modifications to the databases.

Study of opioid overdose deaths provides insight into those at risk because of opioid use, and provides important insights to providers and researchers. Study of deaths from opioid overdose among older adults will improve care for a group who face significant health challenges. The overdose death study will also shed light on differences by sex in the use of opioids.

CHAPTER 2

THE UTAH ALL PAYER CLAIMS DATABASE AND OPIOID PRESCRIPTION GUIDELINES

2.1 Abstract

Utah is considering changes to prescribing guidelines for providers who treat patients with opioids. More restrictive guidelines would encourage providers to reevaluate the care and progress of patients who take more opioids than are specified in a threshold value. Quantities of opioids dispensed in Utah vary between the sexes and between different age groups. An analysis of a statewide database of prescriptions dispensed provides insight into patterns of opioid use and suggests ways in which future data releases could improve research.

2.2 Introduction

Opioid prescribing guidelines are one response to prescription opioid abuse.[22] Morphine equivalent doses (MEDs) provide a common unit to compare different opioids. Values are typically calculated by finding a dose of the opioid that is equivalent to 10 mg of parenteral morphine. Prescribing guidelines often specify a

threshold MED, measured in milligrams per day (mg/d MED), which requires additional action for patients who are prescribed above that dose. This study uses the CDC Injury Center Morphine Milligram Equivalent Table of June 2015 as the baseline for comparisons. MEDs will be used as a common standard to analyze prescribing practices. A 2011 study by Bohnert et al. found that "higher opioid doses were associated with increased risk of opioid overdose death" among patients being treated for pain.[23]

Issued in 2009,[3] the current Utah guidelines urge "clinical vigilance" for higher opioid doses. The authors found no evidence-based definition of a high dose, but recommend the equivalent of 120 mg/d MED as the threshold that should trigger a consultation between patient and provider about the pain treatment plan.

The Washington state guidelines recommend a threshold of 120 mg/d MED per patient[21] and cite a 2010 cohort study in support.[24] Ohio's guidelines recommend a threshold of 80 mg/d MED and state that the odds of overdose are significantly higher above that level.[20] In 2015 the Centers for Disease Control and Prevention (CDC) announced plans to publish prescribing guidelines. Suggested threshold values included 50 and 90 mg/d MED.

2.3 Methods

The Utah All Payer Claims Database (APCD) collects medical and pharmacy claims data from healthcare insurance providers to promote transparency in healthcare spending.[25] Payers of health care expenses submit data to the Utah APCD using a Data Submission Guide.[26] Payers help create quality checks and validity

measures. Data collection can be tailored to the needs of individual payers. Approaches to data quality appear sound, but it is not clear whether there are deviations in reporting between payers. Data can be rejected if standards are not met, which motivates payers to perform quality assurance on their data. Data quality may vary depending on payers' resources.

In Utah, APCD includes data on pharmacy claims paid in Utah except for some Medicare and Medicaid claims. A deidentified APCD data extract was released in 2014, including data from January 2011 to August 2013. Data were obtained by agreement with the Utah Department of Health (UDOH).

The study uses a cross-sectional analysis of the 2014 release to explore the impact of potential changes in prescribing guidelines on dispensing in Utah. The study population consists of those persons who received opioid prescriptions recorded in the APCD.

APCD procedures for collecting and processing data were significantly revised in 2013 (email communication from C. W. Hawley, MA, March 2015). A vendor with responsibilities for the data is no longer in business, complicating efforts to address anomalies in the data. Initial review of the data revealed several issues, described below.

It is not possible to identify the number of unique patients represented in the data extract, which means that in many cases, multiple prescriptions are likely to have been filled for the same person.

Values for dispensed quantity and days' supply are sometimes negative, which is not meaningful in this context. These records were excluded from the data set

before analysis (see Figure 2.1).

Values for days' supply range from 0 to 999. A 0 value made it impossible to calculate the MED. Data managers often use 999 to represent missing or unknown values, and this may have been the case here. Therefore, records with days' supply equal to 0 or 999 were excluded.

The dispensed quantity variable identifies the number of pills dispensed. Some records included a noninteger value for this variable. Because these values could not be interpreted, these records were excluded.

Some prescriptions did not appear to have been prescribed for ordinary pain relief and were excluded. Cough syrups with opioids can be abused, but would not likely be prescribed strictly for analgesia. Other drugs in this category include opioids used mainly for anesthesia, some drugs used for breakthrough pain in cancer patients, and drugs for opioid-tolerant or opioid-experienced patients. A list of these drugs appears in the Appendix. Drugs used for breakthrough pain include some formulations of fentanyl designed for immediate release of the medication. Drugs for opioid-tolerant patients include some formulations of buprenorphine, hydromorphone, and morphine, and some drugs administered by injection. Drugs used for anesthesia, breakthrough pain, or opioid-tolerant patients were identified by a review of indications for drugs as stated by manufacturers or elsewhere in the literature.

Some records did not include the strength of the drug, so daily doses could not be calculated; those prescriptions were excluded. Overall approximately 30% of the opioid prescriptions in the data were excluded (see Figure 2.1).

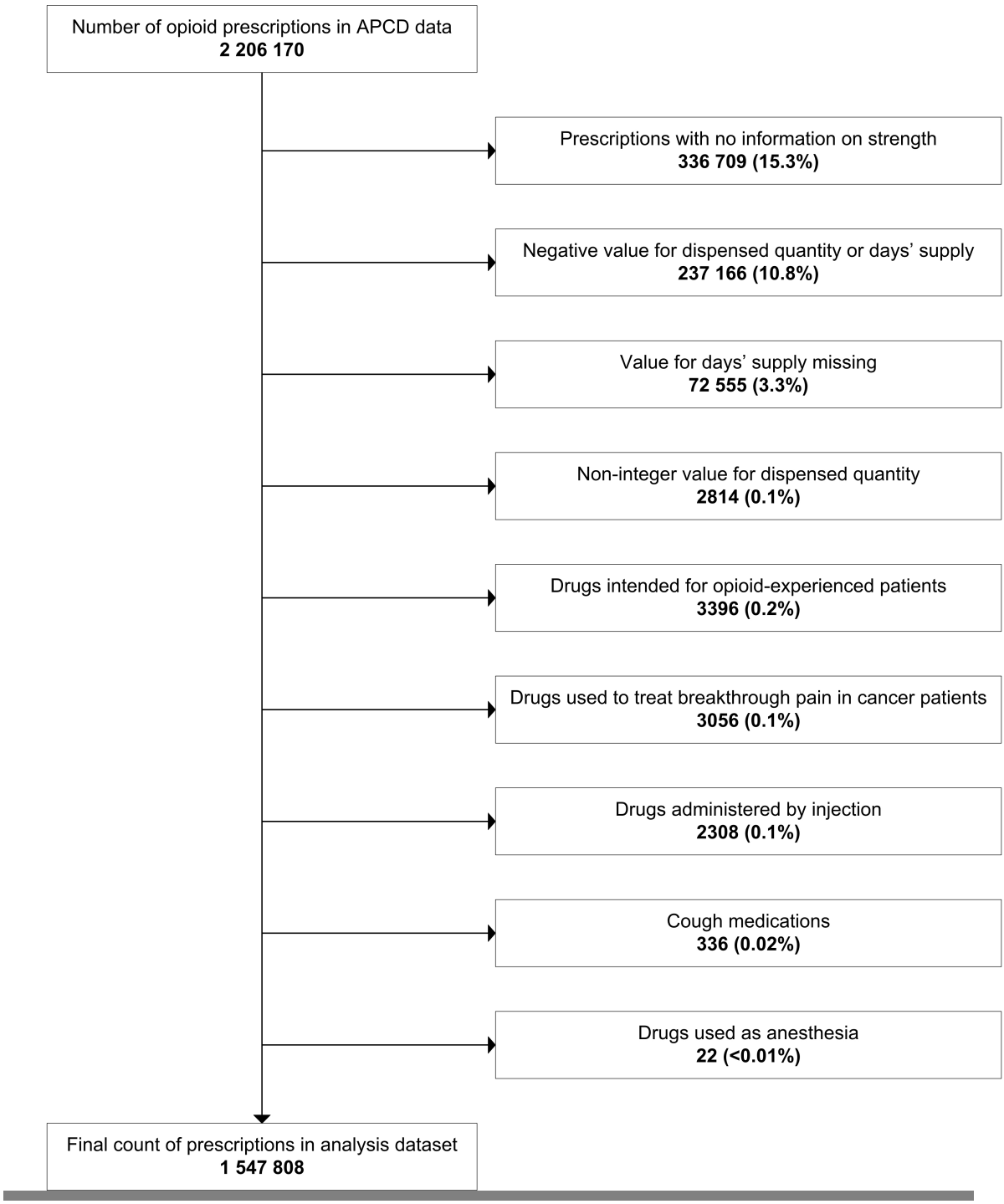

Figure 2.1. APCD records excluded from analysis dataset. Each entry lists the count of prescriptions excluded in that category and the percentage of the original data represented by the count.

MEDs for all drugs except fentanyl were calculated using conversion factors in the Centers for Disease Control and Prevention (CDC) morphine milligram equivalent table from June 2015 (provided by C. A. Porucznik, PhD, in email communication, June 2015). MEDs for fentanyl were calculated with an application created by the New York City Department of Health and Mental Hygiene (Table 2.1),[27] using a study by Von Korff et al.[28]

Measures explored the difference that more restrictive opioid prescribing guidelines would make in Utah's prescribing practices. Prescriptions were tabulated by drug and MED value. Distributions of drugs dispensed at each MED value were compared using a chi-square analysis. Graphical presentations were generated to facilitate comparisons. Prescriptions dispensed to men and women were compared by a chi-square test of proportions based on whether prescriptions were greater than or less than 120 mg/d MED. Drugs were also ranked according to

Table 2.1. Fentanyl dosages and morphine milligram equivalents

Fentanyl dosage in mcg/hour	Morphine milligram equivalent
12.5	30
25	60
50	120
75	180
100	240

how often they were prescribed to men and women at different MED values. Prescriptions were tabulated based on patient age groups, and the proportion of prescriptions for patients in an age group was compared to the group's proportion of the adult population. A chi-square analysis compared prescriptions dispensed by age and by sex.

Where factors such as sex and prescription MED values were associated, actual numbers of prescriptions were compared with expected numbers under an assumption of independence to investigate possible explanations for the observed differences.

2.4 Results

Prescriptions for hydrocodone, oxycodone, and tramadol together represented more than 85% of records (Table 2.2; Figure 2.2). Prescriptions with mg/d MED value greater than 120 represent 12.6% of the records; greater than 90, 21.0%; greater than 80, 23.0%, almost double the percentage greater than 120; greater than 50, 44.4% (Table 2.3). MED > 50 mg/d prescriptions represent more than three times the percentage of MED > 120 mg/d prescriptions. Chi-square analyses for prescriptions at all of the MED levels show significant differences in the distribution of drugs at each level ($p < .001$ in each case).

Women received a higher proportion of prescriptions than men (58.4% vs. 41.6%, $p < .001$). In 2010, women represented just under half the Utah population (49.8%).[29] If there were no relation between sex and opioid usage, we would expect drugs to be dispensed proportionally to the population sex ratio. The disparity here

Table 2.2. Counts and percentages of APCD prescriptions

	Prescription frequency	Percent of prescriptions
Buprenorphine	13 032	0.84
Codeine	970	0.06
Fentanyl	55 283	3.57
Hydrocodone	635 662	41.07
Hydromorphone	18 366	1.19
Meperidine	4715	0.30
Methadone	25 391	1.64
Morphine	80 186	5.18
Oxycodone	498 625	32.21
Oxymorphone	9993	0.65
Tapentadol	5876	0.38
Tramadol	199 709	12.90
Total	1 547 808	100

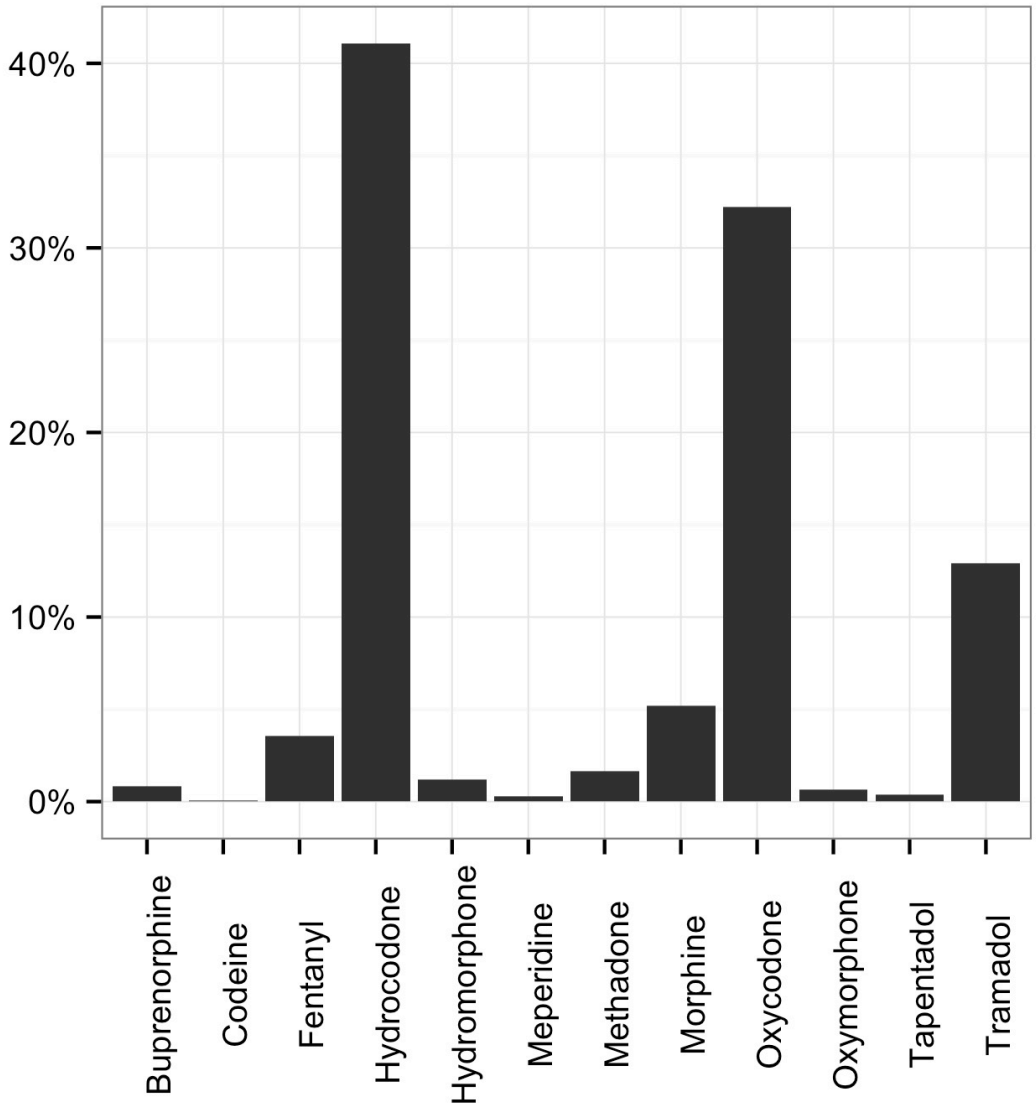

Figure 2.2. Percent of each opioid dispensed

Table 2.3. Counts and percentages of APCD prescriptions based on mg/d MED value

	≥ 50 mg/d MED	**≥ 80 mg/d MED**	**≥ 90 mg/d MED**	**≥ 120 mg/d MED**
Buprenorphine	8937 (1.3)	7724 (2.2)	6365 (2.0)	6178 (3.2)
Codeine	76 (0.0)	10 (0.0)	9 (0.0)	0 (0.0)
Fentanyl	28 146 (4.1)	16 276 (4.6)	12 186 (3.8)	6660 (3.4)
Hydrocodone	198 491 (28.9)	51 903 (14.6)	36 020 (11.1)	18 345 (9.4)
Hydromorphone	13 319 (1.9)	9928 (2.8)	8753 (2.7)	4970 (2.6)
Meperidine	909 (0.1)	176 (0.1)	133 (0.04)	91 (0.05)
Methadone	20 345 (3.0)	17 313 (4.9)	17 271 (5.3)	12 789 (6.6)
Morphine	54 968 (8.0)	37 972 (10.7)	37 434 (11.5)	24 305 (12.5)
Oxycodone	341 092 (49.7)	201 311 (56.7)	194 183 (59.8)	110 678 (57.0)
Oxymorphone	8912 (1.3)	7230 (2.0)	7216 (2.2)	5771 (3.0)
Tapentadol	5384 (1.0)	5170 (1.5)	4838 (1.5)	4387 (2.3)
Tramadol	6166 (1.0)	223 (0.1)	172 (0.1)	87 (0.04)

Table 2.3 continued

	≥ 50 mg/d MED	**≥ 80 mg/d MED**	**≥ 90 mg/d MED**	**≥ 120 mg/d MED**
Total	686 745 (100.0)	355 236 (100.0)	324 580 (100.0)	194 261 (100.0)

suggests that women receive a disproportionate number of prescriptions.

A chi-square analysis shows that patient sex and whether prescriptions were greater than or less than 120 mg/d MED are associated ($p < .001$). Comparing the observed number of prescriptions with the expected if sex were independent of MED value shows that women have more prescriptions than would be expected in the mg/d MED < 120 category, while men have more prescriptions than would be expected in the mg/d MED > 120 category.

Plots that display drugs dispensed by sex show striking similarities. Among all prescriptions (Figure 2.3), rankings of drugs by number of prescriptions for men and women are identical except that hydromorphone and buprenorphine exchange places: women have more hydromorphone than buprenorphine prescriptions, and for men the order is reversed. Dispensing of drugs to men and women was also examined at the mg/d MED levels under consideration here, but there were no important distinctions on which to comment.

APCD records were combined into four age categories corresponding to those in the US Census (Table 2.4). The analysis based on age is limited to prescriptions dispensed to adults. Children represent almost 32% of the Utah population[29] but received less than 3% of the prescriptions recorded. Slightly more than 17% of prescriptions were dispensed to patients 65 or older, although this group represents only 13.2% of the Utah adult population.[29] Since the APCD data do not include information on most prescriptions paid through Medicare, the number of prescriptions available for this analysis is certainly less than the total number of opioids dispensed to older adults. Based on the proportion of older adults in the

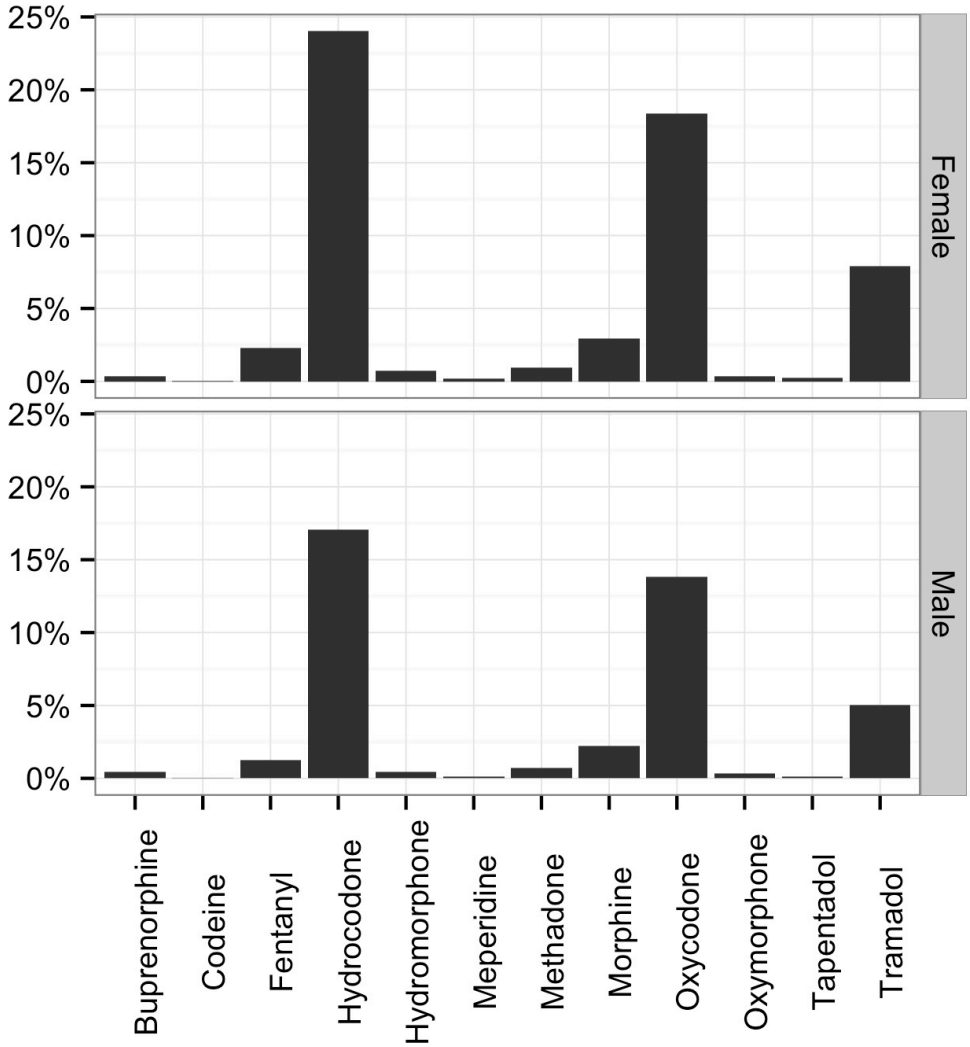

Figure 2.3. Percent of prescriptions by drug for male and female patients

Table 2.4. APCD prescriptions dispensed to adults by age category by counts (percent)

	Utah adult population	**All prescriptions**	**MED ≥ 50 mg/d**	**MED ≥ 80 mg/d**	**MED ≥ 90 mg/d**	**MED ≥ 120 mg/d**
Young adult	1 096 091	572 322	259 174	126 580	116 857	69 410
18-44	(57.9)	(37.9)	(38.7)	(36.6)	(37.1)	(37.1)
Mid adult	547 205	680 456	317 398	173 089	158 143	94 976
45-64	(28.9)	(45.0)	(47.4)	(50.1)	(50.2)	(50.7)
Older adult	249 462	259 224	93 028	45 876	40 311	22 810
65+	(13.2)	(17.1)	(13.9)	(13.3)	(12.8)	(12.2)
Total	1 892 858	1 512 002	669 600	345 545	315 311	187 196
	(100.0)	(100.0)	(100.0)	(100.0)	(100.0)	(100.0)

Utah population and the proportion of opioids dispensed to them in the APCD data, it appears that older adults are dispensed opioid medications disproportionately. The majority of opioids (1 552 778 or 82.9%) were dispensed to patients between 18 and 64.

The prescriptions as a whole and at each MED level are associated with the age categories ($p < .001$ for each comparison). For prescriptions with mg/d MED > 120, mg/d MED > 90, and mg/d MED > 80, higher than expected numbers are found for children and ages birth to 45 to 64. For mg/d MED > 50, higher than expected numbers are found for all decedents except older adults.

Adults aged 45 to 64 represent less than 30% of the Utah adult population, but received almost half (45%) of all opioid prescriptions recorded in APCD for adults and slightly more than half of MED > 120 mg/d, MED > 90 mg/d, and MED > 80 mg/d prescriptions. Adults age 18 to 44 consistently received percentages of prescriptions lower than their percentage of the adult population. Adults 65 and older represent 13.2% of the adult population and received 17.1% of overall prescriptions, but lower percentages in the higher MED categories. The results for adults 65 and older would change in a dataset that included complete Medicare claims data.

A chi-square analysis for the MED prescription levels demonstrates that age and sex are not independent ($p < .001$). For MED > 120 mg/d, more prescriptions than expected appear among women 55 and older and among men under 45. For MED > 90 mg/d, more prescriptions than expected appear among women 65 and older, and among men 18 to 64. For MED > 80 mg/d, more prescriptions than expected appear

among women 65 and older, and among men ages 18 to 64. For MED > 50 mg/d, more prescriptions than expected appear among female young adults and older adults, and among male mid adults.

2.5 Discussion

Lowering the MED threshold in the Utah opioid prescribing guidelines would likely increase demands on provider time and other resources and could reduce provider flexibility in treating patients. Oversight for patients using opioids should include comprehensive evaluation, consideration of alternatives, a written treatment plan, and screening for abuse or addiction. The current Utah guidelines recommend consultation about the treatment plan when prescriptions are above the MED 120 level. Additional consultations could represent a significant time investment. As noted, MED > 50 mg/d prescriptions represent more than three times the percentage of MED > 120 mg/d prescriptions.

Under a MED > 50 mg/d threshold, more than 40% of patients would need further consultation with their providers. This additional time could be a valuable investment if it led to improved care. For some opioid users, the current Utah guidelines encourage drug screening and sleep studies, additional resources that would be affected by a change in a threshold MED level.

A Washington study examined outcomes after the state's adoption of the 120 mg/d MED value.[30] Positive results included decreases in opioid doses, in the percentage of patients who become chronic opioid users, and in deaths. The authors also observed that the rate of overdoses leveled off. However, most overdoses

occurred among patients who were not chronic users and at doses below the 120 mg/d MED threshold. Methadone overdoses increased after the guidelines were created, and many who experienced opioid overdoses also took sedatives. The authors recommend that guidelines address at-risk patients who are not chronic opioid users, patients who overdose at doses lower than an accepted threshold, and other medications prescribed to patients.

The utility of prescribing guidelines remains uncertain. The authors of a 2014 study argued that risk of abuse can be reduced by using guidelines that include detailed assessment and monitoring of the patient.[31] In some cases, guidelines are not followed,[32] or physicians are not wholly convinced by evidence supporting them.[33]

Basing guidelines on MEDs may be problematic. Researchers have criticized opioid equivalence tables, which rely on MEDs, for inconsistencies in the equivalences stated in different tables.[34,35] MEDs should reflect the bioavailability and half-life of active metabolites of drugs, but often do not do so. Comparative effects can be established through clinical trials,[36] but are sometimes determined empirically through a practitioner's experience. Researchers and providers should promote standardization of MEDs and a reliable reference for comparisons.

Oxycodone's dominance in high MED-value prescriptions accords with its status as the drug most often associated with fatal overdose in Utah populations during the years 2000-2012.[37] In 2012 oxycodone was implicated in 52.8% of prescription pain medication deaths in Utah, although it represents only 32.2% of prescriptions in the APCD data.[37] High levels of oxycodone use are significant from a policy

standpoint because research found a rise in heroin use after one formulation of oxycodone was changed to enhance abuse deterrence.[38]

Hydrocodone represents 41% of prescriptions in the APCD data for the drugs examined here, the largest percentage. Attention to more potent drugs may divert attention from drugs such as hydrocodone that are also subject to abuse and that may be gateway drugs to stronger opioids. Some hydrocodone prescriptions could likely be replaced by less potent analgesics.

The data suggest that providers prescribe similarly for men and women. Men and women differ with respect to the analgesic effects of opioids[39-42] and with respect to patterns of use[43-45] and misuse [14,46] of opioids. A recent study of other Utah data found different distributions of drugs implicated in opioid overdose deaths among men and women.[47] Further, information about sex differences is an important element of a comprehensive approach to pain relief and drug abuse. Men receive a disproportionate number of high-MED prescriptions, while women receive a disproportionate number of low-MED prescriptions.

Almost 4% of the MED > 120 mg/d prescriptions were dispensed to children. This is a great deal of medication for a child and could represent opioids prescribed for palliative care or drugs that were diverted. The uncertainty in such a situation highlights why including a diagnosis or indication with prescription information would be useful in PDMP or APCD data.

Adults ages 45-64 receive proportionally more opioids than would be expected based on their population percentage. Research and interventions should target this group to identify factors that increase opioid usage, including age-related

conditions that cause pain.

Patients age 65 and older also receive more prescriptions than expected. The APCD figures underestimate opioid use in older adults because most Medicare claims are not included. Previous research showed that older adults are often undertreated for pain,[16] and that they may obtain medication to abuse or sell it.[48] Research should investigate numbers of prescriptions suitable for this group's needs and diversion of medication prescribed for them.

When age and sex are considered together in relation to high-MED prescriptions, differences between expected values and actual numbers of prescriptions are not always large, but an overall pattern appears. For prescriptions with MED values of 80 or greater, younger men and older women consume more opioids than expected if age and sex were independent in relation to prescriptions.

The study benefits from a large dataset with much information about Utah dispensing during the years 2011-2013. Since most insured residents are covered through an employer, the variety of carriers supplying data implies that different occupations and sociodemographic groups are represented in the data. The patients have a broad range of ages.

There are limitations related to data contents and quality. There is no information on prescriptions paid for in cash. The data present an incomplete portrait of opioid use among Utahns insured through Medicare and Medicaid. The lack of unique patient identifiers limits conclusions that can be drawn about demographic factors in relation to prescription records and about patterns of individual use.

2.6 Conclusion

A lower MED threshold would recommend that providers spend more time with patients who take opioids. The MED values explored here would affect 21% to 44% of prescriptions. While the percentages of patients involved would probably be lower because of multiple prescriptions, lowering the MED threshold implies an increase in provider time with patients. This change would affect provider schedules, particularly for those who specialize in pain management and for primary care providers, who write the majority of opioid prescriptions.[49] The impact of the Washington guidelines offers a cautionary note that no single threshold value will eliminate opioid overdoses and deaths.[30]

Women are dispensed a higher proportion of opioid prescriptions than their proportion of the population. Providers tend to dispense opioids similarly to men and women. Research into different effects of opioids on men and women may challenge this practice.

The data present an incomplete picture of opioid prescribing to older adults, but suggest they are prescribed a disproportionately large amount of opioids relative to their proportion of the population. Their medication should be carefully monitored.

Most opioids are dispensed to patients between 18 and 64. The older members of this group are dispensed a proportion of opioids that is more than double their proportion of the population. Opioid use among this group should be studied to determine motivations and to investigate the use of other analgesics or nonpharmaceutical methods.

The value of the APCD data could be improved. Anonymous individual

identifiers would allow researchers to study the number of prescriptions dispensed to individuals, while protecting their privacy. Dispensed prescriptions could also be compared with data in the PDMP. Such a comparison would require caution to protect patient privacy, but would indicate whether the monitoring program affects the amount of drugs acquired by patients. Greater attention to data quality and content will strengthen conclusions drawn from the data.

CHAPTER 3

THE NATIONAL VIOLENT DEATH REPORTING SYSTEM AND OPIOID DEATHS IN UTAH

3.1 Abstract

Data on opioid overdose deaths in Utah reveal important information on opioid use. Oxycodone is the drug most commonly involved in opioid-related deaths. Men and women differ in which drugs they have taken and how they were obtained. Methadone, usually prescribed as part of an opioid treatment program, plays a significant role in accidental deaths. Hydrocodone, sometimes regarded as a safer alternative to drugs such as oxycodone, is often involved in deaths, particularly among women and in accidental deaths. Tramadol is less strictly regulated than many other opioids, but is a factor in many deaths.

3.2 Introduction

Methods developed to study opioid abuse include collecting information on deaths in which opioid use was a factor. The National Violent Death Reporting System (NVDRS) was created in 2002 and now operates in Utah and 32 other states.[50] Data from NVDRS inform strategies to prevent violent deaths and to

evaluate those efforts. Data are collected on all recognized violent deaths.

NVDRS data come from vital records, such as death certificates, law enforcement agency reports, crime laboratory data, and medical examiner or coroner investigations. The information includes data about the context of each death. The Utah Department of Health's (UDOH) addition of drug overdose data to NVDRS records led to an award for innovation by a national safe practices organization.

Suicide is a specific focus of public health in Utah. The state has one of the highest age-adjusted suicide rates in the US, and suicide is the seventh most common cause of death for Utahns age 10 and older.[51] Information from NVDRS data that sheds light on the problem of suicide in Utah would be valuable.

A primary focus of this study is how deaths among men differ from deaths among women. The relationship between sex, gender, and opioid use is complex. Research may focus on sex differences, as determined by biology, or gender differences, as determined by cultural and identity factors.[52] This study focuses on sex differences because the NVDRS data include limited information on gender identity.

Sex differences are evident in many aspects of opioid use. One study identified mechanisms that could account for differences between the sexes in response to opioid use.[53] A meta-review of 50 studies found no association between sex and analgesia in the use of opioids that act on mu receptors, but observed a greater analgesic effect in women for patient-controlled analgesia.[54]

A longitudinal study found differences between men and women in long-term follow up and in motivations for seeking treatment for opioid addiction.[55] The

authors also found that women with addiction had significantly larger financial and medical needs in treatment and concluded that sex differences must be addressed in efforts to prevent and treat opioid dependence. Another study suggested that different risk factors may influence women and men to misuse opioids.[56] Women are more likely to be influenced by emotional issues including affective distress. Men are likely to be at risk because of legal problems and behavioral issues.

Sex may also affect treatment for opioid misuse. Opioid receptor antagonists are drugs used to treat addiction by blocking the effects of opioids. Roche and King note that women may experience larger hormonal and subjective responses to opioid antagonists than men.[57]

Research suggests some considerations for sex-based interventions. Women who are addicted to opioids are likely to have more serious problems related to their drug use and its effect on their employment.[58] Another study recommends that men be observed for unusual behavior and women be evaluated for the physical and psychological effects of pain.[59] Sex is thus an important aspect of opioid use, and data on opioid users should be studied in relation to sex.

3.3 Methods

NVDRS data are collected and managed according to a process mandated by CDC.[60] In Utah, data are collected at UDOH from primary sources and uploaded to CDC each week. NVDRS addresses data quality issues with standards that include definitions, manuals, and training provided by CDC. Data are checked twice for quality before transmission to CDC, which selects and reviews random records to

identify errors and check for consistency.

The Utah NVDRS data in this study document violent deaths from 2005 to 2012 with records for 6663 unique decedents. Opioids were involved in 1643 nonhomicide deaths. The data include information about investigations of the deaths and demographic data about the decedents.

The study population consists of Utah decedents during the years 2005-2012 whose deaths involved opioids. The decedents form a retrospective cohort of persons who were exposed to opioids before death. The study population cannot be considered the actual population because some opioid-related deaths may not appear in the NVDRS data.

The data were obtained by agreement with UDOH. The Centers for Disease Control and Prevention (CDC), which directs the nationwide NVDRS project, created requirements for data submission. Individuals and incidents have unique identification numbers that help track multiple causes of death that may include combinations of drugs or causes of death not related to drugs. For this study, the term "single-cause death" refers to a death caused only by opioids. Data collection has changed over time as new variables are included. For example, variables to indicate sexual orientation and transgender status were added in 2011.

The NVDRS data present few analytical challenges. The data combine information from sources including medical examiner reports, law enforcement documents, and death certificates. Different sources sometimes disagree about matters such as whether a death should be classified as a suicide. Data are sometimes missing, although this is rare; for example, only one of the opioid-related

decedents does not have an entry for sex or age. The most common category for race after white is “other,” interpreted to mean people of mixed race.

Measures for the study include descriptive statistics that examine sex, age, marital status, race, ethnicity, and homelessness among the decedents. Proportions for these categories were compared with values for the general Utah population. Decedents were classed into age groups based on groupings used by the Census: children (< 18 years), young adults (18-44), mid adults (45-64), and older adults (65 and older). The proportions of different drugs present in suicide and nonsuicide deaths were reported for single- and multiple-cause deaths. Drugs used by male and female decedents were compared in a chi-square analysis and ranked for men and women, according to how often each was involved in both suicide and nonsuicide deaths. Men and women were compared in a chi-square analysis for suicide and nonsuicide deaths by whether drugs were obtained for the decedent or for another person.

The analysis results are used to illuminate general phenomena among the decedents and to suggest further investigation and policy measures that could help reduce deaths by opioid overdose.

3.4 Results

The data include records on 1643 decedents whose deaths involved prescription opioids. Decedents include comparable numbers of women (803, 48.9%) and men (839, 51.1%; Table 3.1). The majority of decedents were either between the ages of 18 and 44 (901, 54.9%) or between 45 and 64 (680, 41.4%). More than 97% of

Table 3.1. Female and male decedents by classification of opioid-related death, count and (percent)[a]

	Female	**Male**	**Total**
Not suicide	653 (49.3)	671 (50.7)	1324 (100.0)
Suicide	150 (47.2)	168 (52.8)	318 (100.0)
Total	803 (48.9)	839 (51.1)	1642 (100.0)

[a] Total is 1642 because sex is missing for one decedent.

records listed the decedent's race as white, and fewer than 5% of decedents were Hispanic. The decedents were thus more homogeneous with respect to race and ethnicity than the general Utah population, which was 88.6% white and 13.0% Hispanic as of 2010.[61] Fewer than 25% of the deaths involved a single cause of death.

Most decedents (1515, 92.2%) were divorced, married, or never married. A smaller number were separated, single, widowed, or had unknown marital status (128, 7.8%). Men and women were significantly different in their distributions of marital status ($p < .001$), but these differences were large only for the categories married and never married. Women were more likely to be married (41.8% vs. 30.0%), and men were more likely to have never been married (34.5% vs. 16.6%). There was no significant difference in marital status among those who committed suicide ($p = .387$). Homelessness was rare among decedents, with only 22, or 1.3%, so classified. Homelessness and sex were associated ($p = .041$), with the majority of homeless (72.7%) being men.

A visual comparison of all opioids involved in deaths (Figure 3.1) highlights the number of times each drug was a factor. Because some deaths involved more than one drug, the number of drugs represented is larger than the number of unique deaths. The drugs involved in the largest numbers of deaths were oxycodone, methadone, hydrocodone, and morphine.

The medical examiner classified deaths as suicide or nonsuicide. There were 318 suicides in 1643 deaths (19.4%). The proportions of opioids present differed between suicide and nonsuicide deaths. In both categories, the most common

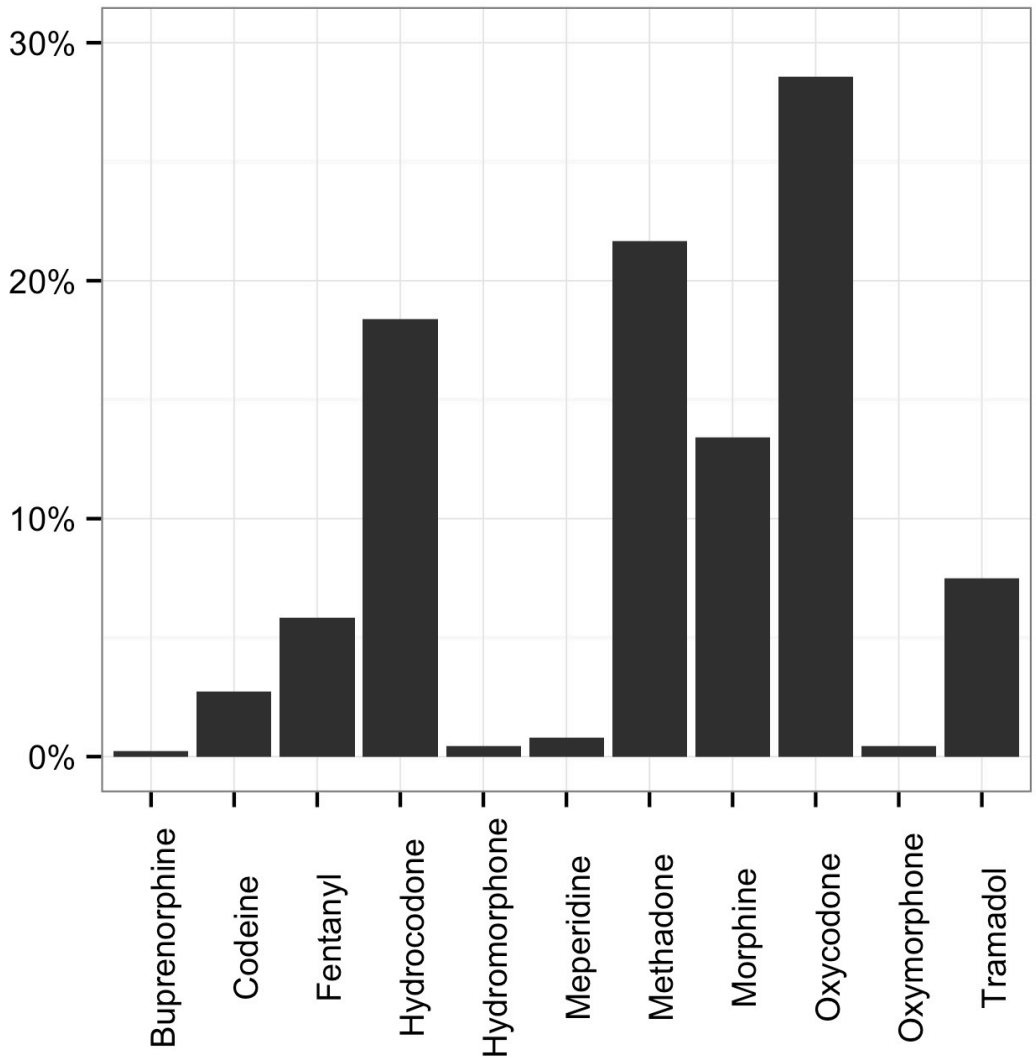

Figure 3.1. Opioids implicated in deaths

opioid was oxycodone. Methadone, hydrocodone, tramadol, and fentanyl were more commonly present in accidental deaths than in suicide.

Single-cause deaths represent 22% of the NVDRS records. The most common opioid involved in these deaths was methadone (Figure 3.2). The next most common opioids in single-cause deaths were oxycodone and morphine. Methadone plays a dominant role in single-cause nonsuicide deaths; it is involved in 41.8% of these deaths. The next most common opioid in these deaths, oxycodone, is involved in 20.7% of deaths, half the number for methadone.

Opioids involved in all deaths differ between men and women (Figure 3.3; $p < .001$). For both sexes the most commonly observed opioid was oxycodone. The next most common drugs were hydrocodone and methadone, but the order differs by sex: hydrocodone was more common in women's deaths and methadone was more common in men's deaths.

Opioids present in suicide deaths also differ by sex. Oxycodone was the most common opioid for both sexes. Although hydrocodone was the second most common opioid in suicide deaths of both sexes, it was more common among women (30.7%) than men (22.0%). Among women, the next most common drugs were tramadol, morphine, and methadone. For men, the next most common drugs were methadone, morphine, and tramadol. The distribution of drugs among suicide deaths of women is again significantly different than that among men ($p = .011$).

The data record whether an opioid was obtained for the decedent or for someone else. Most (56.9%) drugs involved were obtained for the decedent (Table 3.2). The percentages of men and women using drugs that they obtained for

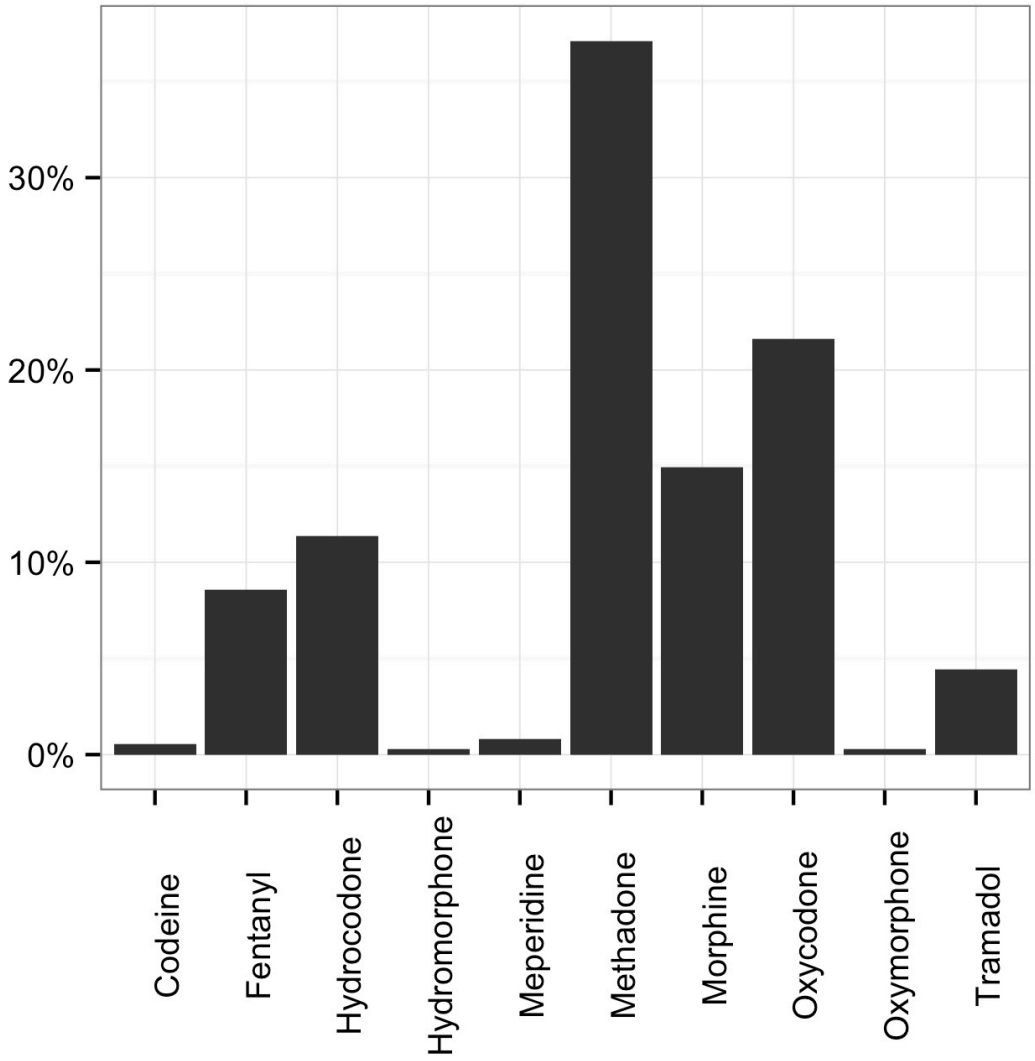

Figure 3.2. Opioids involved in single-cause deaths

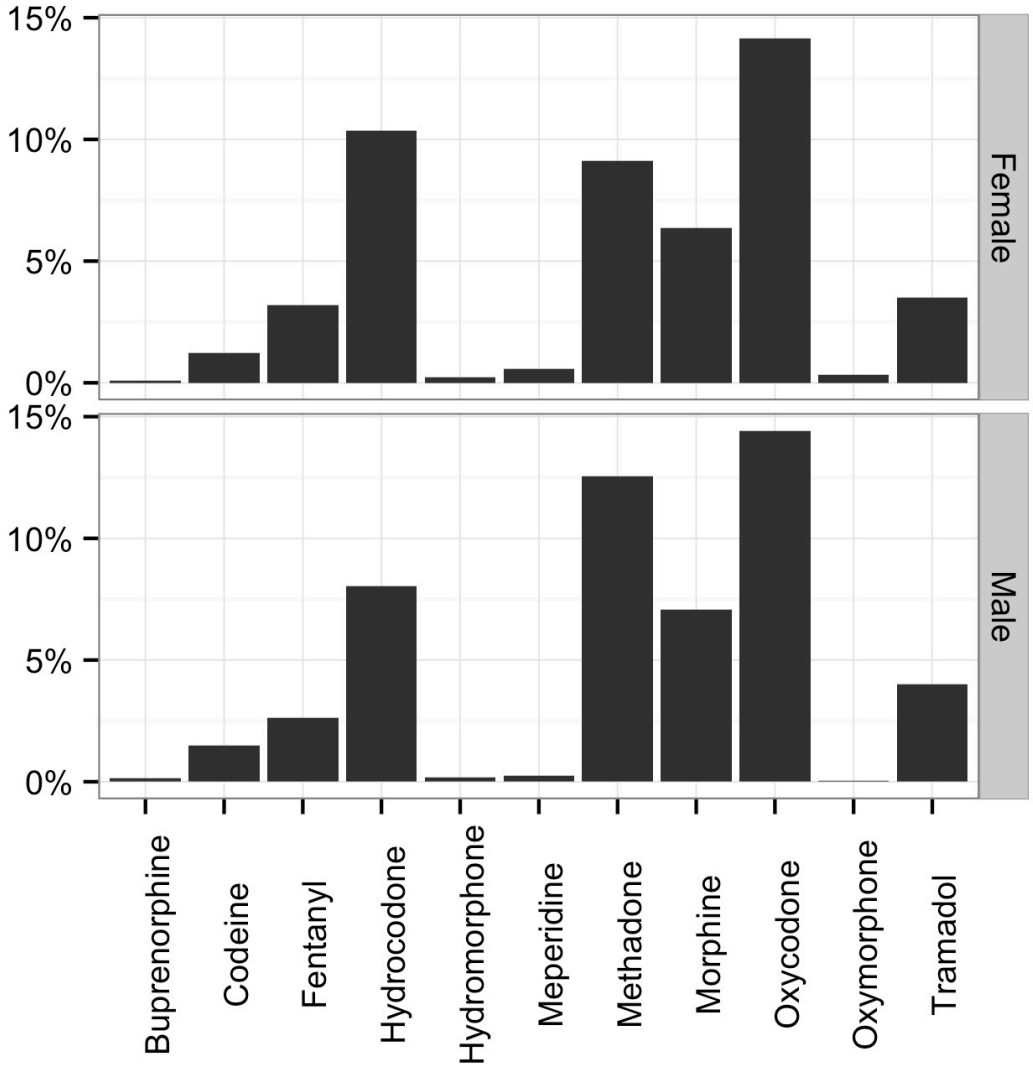

Figure 3.3. Comparison of opioids present in deaths of men and women

Table 3.2. Who the drug was obtained for, all deaths, count and (percent)[a]

	Female	**Male**	**Total**
Drug obtained for self	1499 (61.9)	1147 (51.6)	2646 (57.0)
Drug not obtained for self	924 (38.1)	1076 (48.4)	2000 (43.1)
Total	2423 (100.0)	2223 (100.0)	4646 (100.0)

[a] The total value of 4646 is a count of distinct drugs that appear in decedent records that include the patient's sex.

themselves were significantly different ($p < .001$), with 61.9% for women, and 51.6% for men. Among suicide deaths (Table 3.3), men and women again differ ($p < .001$), but the difference is more pronounced: 61% of women used drugs obtained for themselves, but only 45.5% of men did so. Because men are more likely to die after taking drugs obtained for others, overprescribing opioids to women may increase the risk of death for their male partners or other associates.

3.5 Discussion

Oxycodone has received much attention, and the NVDRS data show that it plays a significant role in opioid overdose deaths. Hydrocodone's impact, particularly among women, is perhaps less expected.

Tramadol is a significant factor in deaths, particularly in suicides. It is the only drug in this study that is classified in the US as a schedule IV controlled substance. Except for buprenorphine, classified in schedule III, the remaining opioids in this study are classified in schedule II. Drugs in schedule IV are judged to have a lower potential for abuse and less danger of creating physical or psychological dependence, compared to drugs in schedule III or schedule II. Tramadol was added to schedule IV in 2014.[62] Tramadol is thus considered less dangerous than many other opioids, yet plays an outsized role in opioid overdose deaths.

Methadone has been used as both a treatment for opioid addiction since the 1960s and an analgesic for chronic, noncancer pain since the mid-1990s.[63] After a steep rise in overdose deaths among patients prescribed methadone for pain, the Food and Drug Administration (FDA) issued a warning about methadone

Table 3.3. Who the drug was obtained for, suicides, count and (percent)[a]

	Female	**Male**	**Total**
Drug obtained for self	309 (61.0)	227 (45.5)	536 (53.3)
Drug not obtained for self	198 (39.1)	272 (54.5)	470 (46.7)
Total	507 (100)	499 (100)	1006 (100.0)

[a] The total value of 1006 is a count of distinct drugs that appear in suicide decedent records that include the patient's sex.

prescriptions in 2006,[63] including revisions to recommended dosages. Compared to other opioids, methadone's risk of toxicity is increased because it has a short duration of analgesia but a longer elimination half-life.[64]

CDC has noted that methadone accounts for a small number of opioid prescriptions, but is involved in a significant number of opioid-related overdose deaths.[63] Utah data reflect these trends. A study of Utah dispensing data found that methadone represented less than 2% of opioid prescriptions.[47] The NVDRS data show that methadone was involved in almost 22% of opioid-related deaths, a disproportionate number. Moreover, methadone was present in 37% of single-cause deaths, compared to 22% (the next-highest percentage) for oxycodone. Most deaths in the NVDRS data that involved methadone were not suicides. Ninety percent of all deaths and 94% of single-cause deaths that involved methadone were not suicides.

Methadone is implicated much less often in suicide deaths than in other types of deaths. In both categories, oxycodone is the most common drug. For nonsuicides, the ratio of oxycodone use to methadone use is 1.1 to 1; for suicide deaths, the ratio is 3.4 to 1. Examining methadone alone reveals that it is implicated more than ten times as often in nonsuicide deaths as it is in suicides.

Special attention to methadone could improve opioid safety. A study by Paulozzi et al. sought to distinguish deaths caused by methadone from those caused by other opioids. The methadone decedents tended to be younger than those who died of other opioids, and fewer than 12% were enrolled in an opiate treatment program.[65] The authors concluded that prescribing methadone requires additional care.

Prescribers, medical examiners, and researchers should have access to information about patients in addiction treatment programs at methadone clinics. Researchers should also track methadone prescriptions. Because methadone plays a larger role in men's than in women's deaths, the drug should be studied to determine whether factors related to sex can explain the different outcomes.

Male decedents are significantly more likely to have used drugs obtained for someone else, especially if they have committed suicide, and are also more likely to have used methadone. Women whose deaths were captured in the NVDRS were less likely than men to have died by suicide, but as likely to have used opioids if they did commit suicide.

The study has a number of strengths. The NVDRS dataset is carefully prepared and managed, and it presents comprehensive information on violent deaths. Among nationwide NVDRS data, the Utah data meet a unique need by gathering information on a class of deaths, drug overdose, which have not been systematically studied as part of NVDRS. The analysis represents an early effort to examine the data for information that could reduce the incidence of overdose and death among those who take opioids.

The most significant limitation in the analysis is the likely omission from the dataset of some deaths caused by opioids because they are not recognized as such. Conclusions about deaths caused by methadone are qualified by the information available about the context of methadone use. Another possible limitation of the study is that the study population is quite homogeneous, even compared with the well-known homogeneity of the Utah population. This aspect of the data raises the

possibility that opioid deaths among some groups are systematically underreported.

3.6 Conclusion

Information about opioid overdose deaths confirms some current ideas, but challenges others. The Utah NVDRS data suggest that focus on oxycodone is reasonable because of its major role in overdose deaths. While hydrocodone and tramadol may be perceived as less risky than other opioids, they are important factors in deaths, which suggests their use should be considered more carefully. Providers and patients should be surveyed about their views on the comparative risks of different opioids. Some drugs that may seem safer than others are implicated in a significant number of deaths.

Hydrocodone is involved in more deaths among women than among men. If hydrocodone is viewed as a safer alternative to drugs like oxycodone, this difference could imply that a patient's sex influences provider thinking about pain management. Providers may feel less comfortable managing women's use of opioids and therefore prescribe "safer" drugs, such as hydrocodone, to treat pain with less perceived risk.

Men's higher likelihood of death after taking drugs obtained for others suggests that overprescribing opioids to women may create situations where partners or relatives divert the opioids and are injured. Further study of sex and opioids will illuminate differences and ways to improve patient care in light of the differences.

NVDRS data offer important insights into accidental deaths. Methadone is involved in many deaths, particularly among men. Evidence suggests that most such

decedents were taking methadone for addiction treatment. Use of methadone should be re-examined to promote safety since a drug prescribed to help patients overcome a dangerous addiction should not increase their risk of death. Hydrocodone and tramadol are likewise involved in many accidental deaths. The fact that they are less potent than some other opioids should not cause complacency about their safe use.

CHAPTER 4

THE NATIONAL VIOLENT DEATH REPORTING SYSTEM AND OPIOID DEATHS AMONG DIFFERENT AGE GROUPS OF THE UTAH POPULATION

4.1 Abstract

Children and older adults who suffer opioid overdoses in Utah are most likely to die after using drugs that were obtained for other people. Deaths in those groups usually involve less potent opioids, such as morphine and hydrocodone. Oxycodone was the most common drug used by other age groups. Deaths among older adults include a high proportion of deaths due to suicide. Data suggest additional contexts for opioid deaths, including decedents' other health issues, cultural factors, and the need to consider other members of a patient's household when treating the patient.

4.2 Introduction

Methods developed to study opioid abuse include collecting information on deaths in which opioid use was a factor. The National Violent Death Reporting System (NVDRS) was created in 2002 and now operates in Utah and 32 other states.[50] Data from NVDRS inform strategies to prevent violent deaths and to

evaluate those efforts. Data are collected on all recognized violent deaths. NVDRS data come from vital records, such as death certificates, law enforcement agency reports, crime laboratory data, and medical examiner or coroner investigations. The information includes data about the context of each death. The Utah Department of Health's (UDOH) addition of drug overdose data to NVDRS records led to an award for innovation by a national safe practices organization.

Suicide is a specific focus of public health in Utah. The state has one of the highest age-adjusted suicide rates in the US, and suicide is the seventh most common cause of death for Utahns age 10 and older.[51] Information from NVDRS data that sheds light on the problem of suicide in Utah would be valuable.

A commentary published after the beginning of the rise in opioid use noted that two populations were particularly at risk from abuse: adolescents, because of the uncertain effect on their future health; and older adults who have a higher sensitivity to opioids' toxic effects.[66]

For this study, older adults are defined as those who are 65 years of age or older. Aging produces changes in opioid pharmacokinetics. These can include changes in absorption rates and decreased metabolism of drugs. Other changes may reduce the first pass effect of opioids and alter elimination of drugs.[67] Such changes can cause opioids to be more potent and to have a longer-lasting effect than expected.[68] Older adults are also at risk for neurological and musculoskeletal side effects of opioids.[69] They have a higher risk of complication from respiratory diseases such as influenza or rhinovirus.[70,71] Combining respiratory difficulties with opioid use for occasional pain relief could cause additional deaths if the respiratory condition and the opioid

use are not carefully tracked.

A study by Inciardi et al. that reported interviews with law enforcement and regulatory officials as well as pill brokers identified older adults as prominent sellers of diverted opioids.[48]

4.3 Methods

The Utah NVDRS data in this study document violent deaths from 2005 to 2012. Records include information for 6663 unique decedents. Opioids were involved in 1643 nonhomicide deaths. The data include information about investigations of the deaths and demographic data about the decedents.

The study population consists of Utah decedents during the years 2005-2012 whose deaths involved opioids. The decedents form a retrospective cohort of persons who were exposed to opioids before death. The study population cannot be considered the actual population because some opioid-related deaths may not appear in the NVDRS data.

The data were obtained by agreement with UDOH. The Centers for Disease Control and Prevention (CDC), which direct the nationwide NVDRS project, created detailed requirements for data submission. Individuals and incidents have unique identification numbers that help track multiple causes of death that may include combinations of drugs or causes of death not related to drugs. For this study, the term "single-cause death" refers to a death caused only by opioids. Data collection has changed over time as new variables are included. For example, variables to indicate sexual orientation and transgender status were added in 2011.

The NVDRS data present few analytical challenges. The data combine information from sources including medical examiner reports, law enforcement documents, and death certificates. Different sources sometimes disagree about matters, such as whether a death should be classified as a suicide. Data are sometimes missing, although this is rare; for example, only one of the opioid-related decedents does not have an entry for sex or age. The most common category for race after white is "other," interpreted to mean people of mixed race.

Measures for the study include descriptive statistics that examine sex, age, marital status, race, ethnicity, and homelessness among the decedents. Decedents were classed into age groups based on groupings used by the Census: children (< 18 years), young adults (18-44), mid adults (45-64), and older adults (65 and older).

The most frequently observed drugs were tabulated by age group for all deaths and for single-cause deaths. The most common drugs found in deaths of older adults were studied specifically. Incidence of suicide was reported by age group and, for older adults, compared with suicides by all methods in that group. Age groups were compared according to whether drugs were obtained for the decedent or for another person, for suicide and nonsuicide deaths.

4.4 Results

The data include records on 1643 decedents whose deaths involved prescription opioids. The decedents include comparable numbers of women (803, 48.9%) and men (839, 51.1%). The majority of decedents were either between the ages of 18 and 44 (901, 54.9%) or between 45 and 64 (680, 41.4%). Only 2.4% of decedents

were age 65 or older (Table 4.1), compared to 9% of the general population in Utah. More than 97% of records listed the decedent's race as white, and fewer than 5% of decedents were Hispanic. The decedents were thus more homogeneous with respect to race and ethnicity than the general Utah population, which was 88.6% White and 13.0% Hispanic as of 2010.[61]

For all age groups, the most common opioids were oxycodone, hydrocodone, methadone, and morphine. Oxycodone was the most common drug found in deaths of young adults and mid adults and the second most common in deaths of children and older adults. Morphine was the most common drug in deaths of children, and hydrocodone the most common among older adults.

Among deaths from a single cause, the most common drugs found in young adults and mid adults are the same as those found in all deaths, but the order of the frequency changes. For both groups, the most common drug was methadone. Among children the most common drug was morphine, and among older adults the most common was hydrocodone.

A visual representation of deaths among older adults (Figure 4.1) highlights the role of hydrocodone. Hydrocodone was a factor in almost twice as many deaths among older adults as oxycodone, the next most common drug. The plot also illustrates the limited number of different opioids that were involved in older adult deaths. A similar plot of single-cause deaths among older adults (Figure 4.2) highlights the role of hydrocodone and tramadol in these deaths and shows that oxycodone was not involved in any deaths in this category.

In all age groups except older adults, suicide deaths represent less than 25% of

Table 4.1. Age distribution of decedents whose deaths were linked to opioid use[a]

Age category	Count (percentage)
Children, < 18	21 (1.3)
Young adults, 18-44	901 (54.9)
Mid adults, 45-64	680 (41.4)
Older adults, 65+	40 (2.4)
Total	1642 (100.0)

[a] Total is 1642 because age is missing for one decedent.

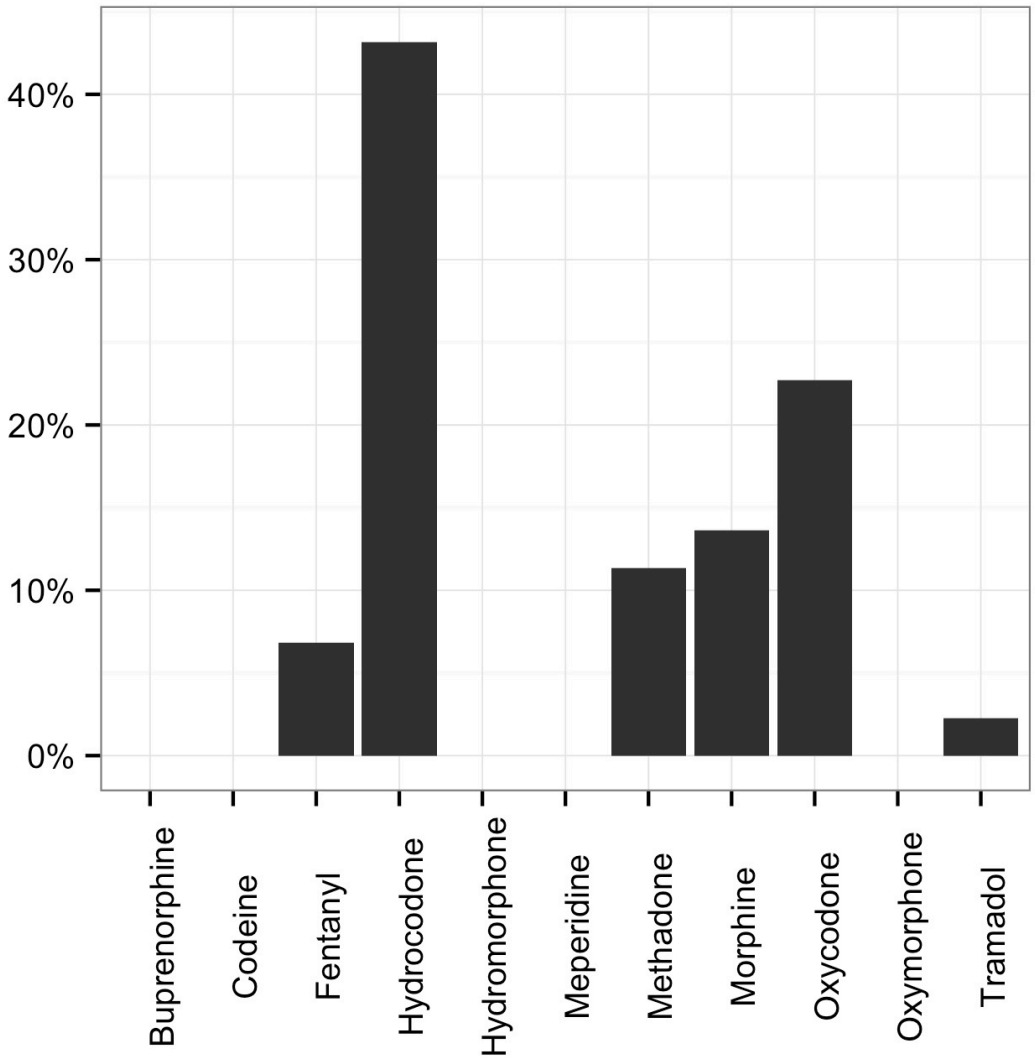

Figure 4.1. Opioids involved in deaths among adults 65 and older

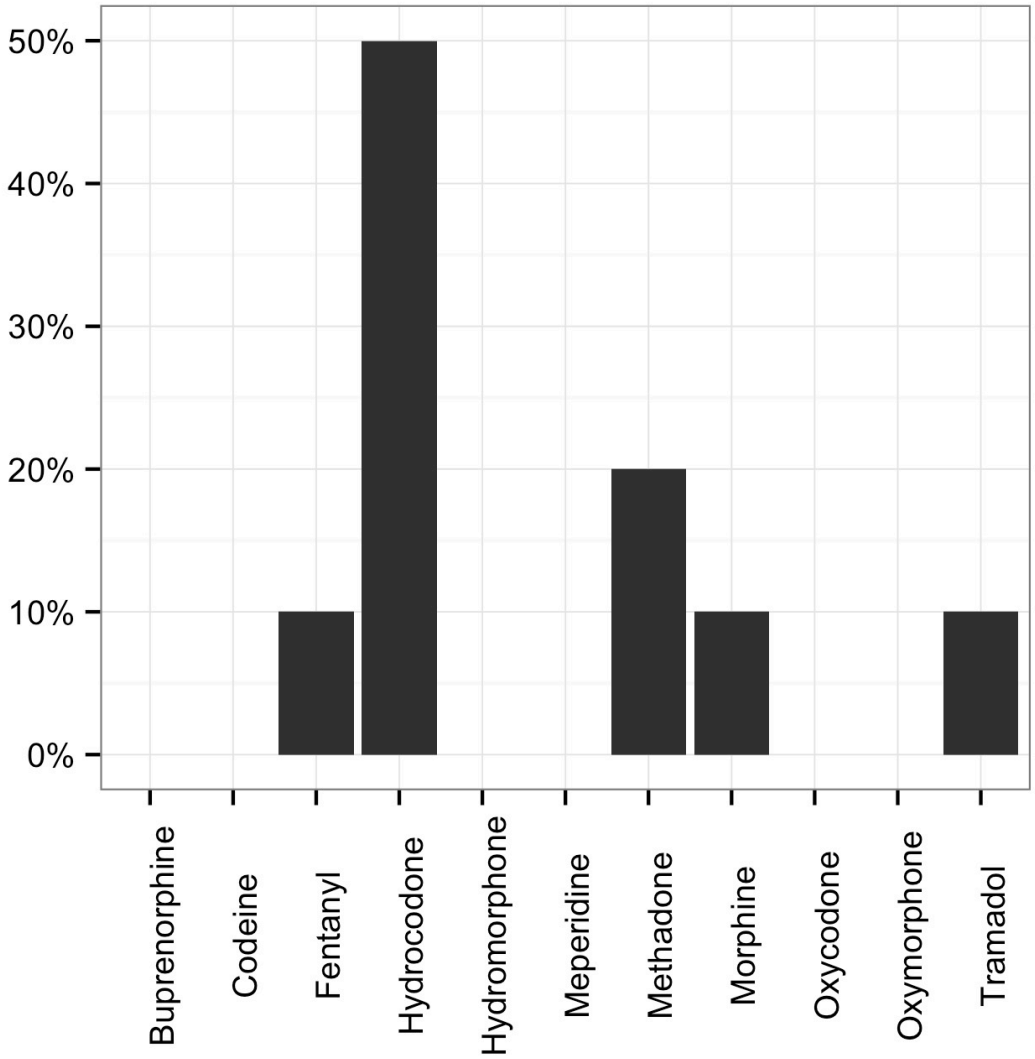

Figure 4.2. Opioids involved in single-cause deaths among adults 65 and older

deaths: 14.3% among children, 15% among young adults, 23.3% among mid adults (Table 4.2). For older adults, half of the deaths were classed as suicides.

The distribution of whether a drug was obtained for someone else is associated with age groups ($p < .001$). Almost three quarters of drugs involved in child deaths were obtained for someone else (74%, Table 4.3). Almost half of drugs involved in an older adult's death were obtained for someone else (49.5%). The corresponding percentages were lower for young adults (45.3%) and mid adults (39.1%). Older adults who committed suicide were much more likely (63.0%, $p = .003$) to have done so using drugs obtained for someone else. Suicide status and who the drug was obtained for were also associated in mid adults ($p = .008$), but in that group decedents who committed suicide were more likely to have used drugs obtained for themselves (56.2%).

4.5 Discussion

The proportion of deaths among older adults is significant. In 2010 an estimated 9% of the Utah population was age 65 or older. The 40 older adult decedents among the NVDRS opioid deaths represent less than 3% of the total. Taken together, these measures suggest that age is associated with death from opioid overdose, and that the true proportion of deaths among older adults is underestimated.

The baby boom generation—Americans born between 1946 and 1964—are now 50 years of age or older. They represent almost 24% of the US population, and are a group habituated to the idea of drug use. Miech et al. studied accidental poisoning deaths from 1968 to 2007.[72] The authors concluded that much of the increase in

Table 4.2. Classification of opioid deaths by age[a]

	Children < 18	**Young adults 18-44**	**Mid adults 45-64**	**Older adults 65+**	**Total**
Not suicide	18 (85.7)	765 (84.9)	521 (76.6)	20 (50.0)	1324 (80.6)
Suicide	3 (14.3)	136 (15.1)	159 (23.4)	20 (50.0)	318 (19.3)
Total	21 (100.0)	901 (100.0)	680 (100.0)	40 (100.0)	1642 (100.0)

[a] Total is 1642 because age is missing for one decedent.

Table 4.3. Who the drug was obtained for, counts (percent)

	Children < 18	**Young adults 18-44**	**Mid adults 45-64**	**Older adults 65+**	**Total**
Obtained for self	13 (26.0)	1373 (54.7)	1212 (60.9)	48 (50.5)	2646 (57.0)
Not obtained for self	37 (74.0)	1139 (45.3)	777 (39.1)	47 (49.5)	2000 (43.1)
Total	50 (100.0)	2512 (100.0)	1989 (100.0)	95 (100.0)	4646 (100.0)

accidental overdose deaths since 2000 is attributable to the rise in use of prescription opioids, but they also found elevated odds for such deaths among baby boomers compared to cohorts of Americans who were either older or younger than boomers.

Baby boomers who use opioids present challenges to drug treatment programs. Some must remodel their facilities to accommodate older patients and provide medical care onsite that had not been needed previously, such as for chronic disease. Older patients who are struggling with addiction must be treated for age-related pain with nonaddictive drugs.[73]

Respiratory disorders complicate opioid use among older adults. Recommendations that older adults be vaccinated against influenza and pneumonia should be re-emphasized in light of the interaction those diseases can have with opioid use. If older adult patients do get a respiratory infection, their medications should be reviewed and they should be cautioned about opioid use during the infection.

Half of opioid-related deaths among older adults were classified as suicides. Of these, almost two thirds took drugs that had been obtained for others. These findings are extremely relevant because many deaths of older adults that are believed to be due to old age or comorbidities may not be investigated by medical examiners. UDOH reported in 2012 that older adults represent 9.3% of the Utah population, 10.7% of suicides in Utah, and 1.7% of suicide attempts.[74] Among the opioid deaths in the NVDRS data set, suicides accounted for 14.3% of child deaths, 15% of young adult deaths, and 23.3% of mid adult deaths. These percentages are

significantly lower than the 50% of deaths classified as suicide among older adults ($p < .001$).

UDOH also found suicide was significantly more common among older men than older women, with 39.3 male suicides per 100,000 of population age 65 or older, versus 4.9 female suicides for the same population. In the NVDRS opioid death data, 70% of older adult suicides are male. This difference in ratio is not as extreme as that cited by UDOH in all older adult suicides, but it is clear that older adult men are at significantly higher risk for suicide than older adult women ($p = .027$).

While older adults represent a small percentage of opioid deaths in the NVDRS data, the percentage of suicides should trigger additional scrutiny of risk factors for them. Older adult men in particular should be screened carefully for depression and other conditions that may interact with opioid use to increase the likelihood of suicide. Since men are more likely than women to die after taking drugs obtained for others, such screening would be useful even if the men have not been prescribed opioids.

Within these data, the percentage of deaths classed as suicide increases monotonically with age, from 14.3% for children to 15.1% for young adults to 23.4% for mid adults to 50% for older adults.

Overdose deaths among older adults involved only six drugs studied here. Overdose prevention and other drug safety efforts that focus on older adults could target those drugs in particular to improve safety.

Hydrocodone is the opioid most often involved in overdose deaths among older adults. This is true of deaths from multiple causes, whether suicide or nonsuicide,

and true of single-cause deaths as well. This may be surprising because of greater public and scientific attention to oxycodone. A PubMed search in July 2015 produced 758 articles that mention "hydrocodone" and 2429 that mention "oxycodone." Moreover, oxycodone's higher morphine equivalence value—1.5 compared to 1 for hydrocodone—may fuel a perception that hydrocodone is less risky than oxycodone and other opioids. Some hydrocodone deaths may be due to liver toxicity caused by combinations of hydrocodone and acetaminophen.

Almost three-quarters of child deaths are associated with drugs obtained for another person. This percentage suggests that interventions to increase safe opioid use—such as education about proper storage and disposal of opioids—could save lives as well as improve health.

The study has a number of strengths. The NVDRS dataset is carefully prepared and managed, and it presents comprehensive information on an important category of deaths. Among nationwide NVDRS data, the Utah data meet a unique need by gathering information on a class of deaths that has not been systematically studied as part of the NVDRS. The analysis represents an early effort to examine the data for information that could reduce the incidence of overdose and death among those who take opioids.

The most significant limitation in the analysis is the omission from the dataset of some deaths caused by opioids because they are not recognized as such. Another limitation is that the most striking findings from the analysis concern children and older adults, whose numbers in the NVDRS data are small: the two groups represent more than 40% of the Utah population, but less than 4% of the NVDRS data.

4.6 Conclusion

NVDRS data yield important insights into opioid use and deaths among different age groups, but the analysis also suggests the need for a wider perspective among researchers and providers.

Oxycodone is the drug most often involved in deaths of young adults and mid adults. However, single-cause deaths among these groups are dominated by methadone. The identity of the drugs most often involved in the deaths of children and older adults, morphine and hydrocodone, may be surprising because those drugs have been considered less risky than more potent formulations of opioids.

Study of drug use in older adults must include a factor not related to the aging process. The baby boom generation forms the majority of the current cohort of American older adults. This group historically has been accepting of drugs and comfortable with assuming risks in drug use to a much greater degree than previous generations, and this pattern continues into their old age.

More generally, the data show the need for a wider context for studying opioid use. Opioids are associated with a heightened risk of suicide among older adults, especially older adult men. Other psychological factors, such as depression, must therefore be considered, as must issues related to addiction. The likely interaction of respiratory conditions and opioids suggests the need for vigilance regarding infections and vaccination among older adults. Respiratory health issues are particularly important for the current cohort of older adults because many of them have been smokers for some part of their lives. The scenario of some older adults selling opioids illegally to supplement their income suggests that issues such as the

cost of living may affect drug use by many members of the community.

Hydrocodone is prominent among deaths of older adults, including those due to suicide or to a single cause. Future research should evaluate whether these deaths are attributable to the opioid effects of hydrocodone alone or to opioid effects and liver toxicity in combination drugs.

Consideration of deaths among the old and the young demonstrates that efforts to address opioid abuse should move beyond a focus on the patient. The patient's household should be considered the unit of risk and the focus for counseling. Children and men often take drugs that are prescribed for others. Household members can observe each other for factors, such as respiratory illness or depression, that may heighten the risks of opioids. Safe storage of drugs should be a priority involving all members of a household in order to protect all. Although many resources have been invested in education about why excess opioids should not be stored, future efforts should explore why this practice persists and how it might be reduced.

CHAPTER 5

CONCLUSION

These data highlight important factors relevant to overuse of opioids and associated morbidity and mortality: different experiences in men and women, the influence of age, and considerations beyond patient care and the effect of drugs. The study also offers insights into the use of administrative and surveillance data in health care research.

5.1 Sex-based issues

Sex plays an important role in efforts to tailor care to individual patient needs. There are important sex-based differences in patients' use and abuse of opioids and in the drugs' analgesic effect. Despite these differences, providers apparently do not consider patient sex when prescribing opioids. Women are more likely to take less potent opioids, but suffer death from overdose in equal proportions to men. Men take stronger opioid formulations and are more likely to die after taking drugs obtained for others. Future research should investigate both behavioral and biological bases for these differences.

5.2 Age-related issues

Treatment should reflect the variable impacts of opioid use among age groups. Older adults appear to take a large number of opioids, but are underrepresented in opioid overdose deaths. They are much more likely to use opioids to commit suicide than younger patients. Providers should evaluate older adult patients for suicide risk and investigate whether opioids prescribed for these patients are actually taken by them.

Children receive the smallest proportion of dispensed opioids, and they represent the smallest category of deaths from overdose. However, they are much more likely to die after taking drugs that were obtained for others than any other age group. Interventions to increase safe storage and disposal of opioids will benefit children's health.

Young and mid age adults take the most opioids, and when they die from overdose, they are least likely to have taken drugs obtained for another person. The large number of opioids taken by this group could be a sign that providers are alert to the dangers of opioids for children and older adults, but are less wary of overuse among young and mid adults. Research on this group should focus on why they consume opioids at the level they do and whether other treatments could be substituted for opioids.

5.3 A wider context for opioid abuse

The experience of the baby boom generation shows that cultural contexts influence health issues throughout patients' lifetimes. Those contexts may seem

remote from medical care, but must be considered as part of effective treatment. For example, providers who treat older adults with opioids must consider their overall health and economic well being.

Safe, effective use of opioids requires that providers understand the patient's context. Patients who take opioids are part of a social network that includes family members and others with whom they live and associate. This perspective would heighten awareness of how the availability of a patient's opioids affects the health of others. Others may be injured by drugs that are not properly stored; they may divert the patient's opioids for their own use or for resale.

All opioids are not alike, but all can damage patient health if used improperly. Much attention has focused on oxycodone. Drugs such as hydrocodone receive less attention, but have caused considerable harm. Neither providers nor patients may have a clear understanding of the risks associated with different opioids. The effects of combination drugs that include hydrocodone demonstrates that patients' opioid use must be considered in light of their other medications.

The link between changes in oxycodone formulation and a rise in heroin use suggests the complexity of abuse issues. When oxycodone became more difficult to abuse, users could have been expected to use stronger opioids such as hydromorphone or fentanyl, rather than heroin. However, heroin might have been more accessible than illicitly obtained prescription drugs, or users might have been influenced by a culture of opioid users who turned to heroin when oxycodone no longer satisfied them.

Despite educational efforts that urge patients to dispose of unused prescription

medication, questions remain about the best way to encourage disposal. This issue is a particular challenge with respect to opioids because they can be sold or traded as well as kept for future use. Further studies should investigate how to motivate safe disposal and what issues may present barriers.

5.4 Opioids and treatment of cancer pain

Research has often assumed a distinction between chronic noncancer pain and cancer pain. Interventional studies may include cancer and noncancer patients to account for the perceived difference.[75] Some researchers and providers have challenged the distinction, suggesting that cancer pain cannot be meaningfully distinguished from other types of pain.[76]

Cancer patients cannot be separated from other patients in the data used in this study. If the distinction between the two categories is accepted, this is a limitation of the study. However, the presence of cancer would be relevant only with respect to the dispensing data used in the APCD study (aim 1). Data in the NVDRS study (aims 2 and 3) come from patients who have died of an opioid overdose. Some of these patients probably suffered from cancer, but it is not clear that their cancer status was related to their deaths. Although recent decades have seen a tremendous increase in opioid use, during much of that period the US has experienced a decline in both cancer death rates and overall incidence rates in men, and stable incidence rates in women.[77] It is not likely that the study's conclusions will be biased by the presence of cancer patients in the patients whose data will be analyzed.

5.5 Data use and quality issues

Data quality is vital in health research because of its implications for patient care. The most important priorities are improving the quality of data and balancing patient privacy with public health interests. Data sharing among researchers, providers, government agencies, and others will stimulate innovation. Better data on prescriptions and adverse events will promote better decisions about opioid use.

This study has compared data files from different processes. The NVDRS process appears to be more consistent and likely more reliable than the APCD process. NVDRS data are compiled by staff at UDOH, which is known to be sophisticated about data management issues. The data quality check by CDC after submission provides a second look that promotes data quality. Communication between states and CDC also allows for iterative improvement of the data collection process.

APCD does not include information about undispensed prescriptions and does not account for different processes in the organizations that supply data. Depending on the carefulness of submissions, some data may be missing, and there may be systematic problems with data from small payers with few resources.

One limitation of the NVDRS process is that a death not recognized as opioid-related is not included. Some data that do not meet the NVDRS standards will be lost, but whether such cases would be systematic is not clear. While UDOH has resources to collect data, the counties that report to UDOH have varying levels of resources to manage their data.

5.6 Conclusion

The rise in opioid use in the US has been accompanied by a complex array of often unpredictable events that have challenged providers, researchers, law enforcement, regulatory agencies, and others. Considerable research has focused on opioid use, but many perplexing questions remain. Future research should include surveys of patients and providers about their attitudes toward different opioids. Researchers should further explore differences in opioid use between sexes and among different age groups. Data scientists should develop linkages between different data sources that protect patient privacy, but allow a more complete account of how individuals use opioids in context. Finally, researchers should continue to investigate connections between opioid use and other aspects of patients' health.

APPENDIX

The drugs listed below were excluded from the All Payer Claims Database study (chapter 2) because they were used for anesthesia or breakthrough pain, administered by injection, or intended for use by patients who were opioid tolerant.

Opioids used for anesthesia or other supervised use

- Fentanyl citrate injection 50 mcg/mL

Opioids used for breakthrough pain in cancer patients

- Fentanyl citrate
- Fentora buccal tablets
- Fentanyl buccal soluble film
- Fentanyl sublingual spray

Injectable opioids

- Buprenex Injection (buprenorphine hydrochloride) 0.3 mg/mL
- Buprenorphine 0.3 mg/mL injection
- Hydromorphone hydrochloride injection: 1 mg/mL; 2 mg/mL; 4 mg/mL; 10 mg/mL; 50 mg/5 mL
- Meperidine hydrochloride injection: 25 mg/mL; 50 mg/mL; 75 mg/mL; 100 mg/mL
- Morphine sulfate injection: 2 mg/mL; 4 mg/mL; 5 mg/mL; 10 mg/mL; 15 mg/mL; 50 mg/mL; 100 mg/10 mL

Opioids for patients who are opioid-tolerant

- Butrans: 10 mcg/hour; 20 mcg/hour
- Morphine sulfate oral solution 100mg/5 mL
- Oxycodone hydrochloride oral solution 20 mg/m

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